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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,311	11/20/2003	John A. Chiorini	14014.0252U3	3284

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,311	CHIORINI ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/18/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,6-28,30-36 and 38-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6-28,30-36 and 38-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 12/18/07 has been acknowledged and fully considered.

Claims 2-3, 6-28, 30-36 and 38-42 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 2-3, 6-28, 30-36 and 38-42 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reason of record as set forth in the office action mailed on 09/18/07.

The scope instant claims encompasses a vector system that comprises variants of AAV4 capsid protein having at least 90% homology to an amino acid sequence set forth in SEQ ID NO:4, and about 98% homology to SEQ ID NO: 4, 16 and 18 (see claim 1).

In addition the scope of invention as claimed further encompasses variants of AAV4 Rep protein having at least 95% homology to amino acid sequences set forth in SEQ ID NO:2, 8, 9, 10 and 11 (see claims 6).

Besides the nucleotide sequence of SEQ ID NO:l, which encodes the AAV4 genome, the AAV4 Rep proteins (SEQ ID NO(s): 2, 8, 9, 10 and 11) and the AAV4

Capsid proteins (SEQ ID NO(s): 4, 16 and 18) the specification as failed fails to disclose any variants of AAV4 Rep and AAV4 Capsid proteins (as claimed).

Response to Argument (Written description)

The applicant argues that the variants as claimed meet USPTO written description guidelines wherein a genus of sequences can be claimed based on sequence identity to a specific sequence (see Example 14 of the U.S.P.T.O. *"Synopsisof Application of Written Description Guidelines")(hereinafter "Synopsis"),* wherein it is stated:

> [t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants...which are capable of the specified catalytic activity.

Regardng the functinal aspect of the variants as calimed the the applicant argues that the present claims are limited by structure, e.g., to nucleic acids encoding an AAV4 capsid protein having at least 90% homology to the amino acid sequence set forth in SEQ ID NO:4.

The applicant further argues that, applicants are not attempting to describe the genus based on a function or a method of identifying the compositions. Rather, every single member of the genus is strictly set forth by the sequence identity limitation. In contrast, the applicant asserts that as shown in the USPTO WD-Synopsis, the fact that a functional limitation is provided such that the skilled artisan can test a construct within the genus to verify function is not equivalent to defining the construct by function. Instead, the construct is clearly defined based on its structure and a function is provided in the specification to allow the artisan to verify its utility. The fact that the claim also include reference to a utility/function, does not alter the fact that the molecules included in the claim are defined by structure as disclosed in the specification the applicant concluded that the present rejection do not apply to the current genus claim (see Remarks especially, pages 9-10).

However the applicant's arguments are found not persuasive because the AAV4 capsid protein variants having at least 90% homology to an amino acid sequence set

forth in SEQ ID NO:4 are not associated with any **specific functional activity** according to the USPTO written description guidelines. Furthermore, as stated earlier that the production of AAV particles is the function of entire vector system, which further depends upon the variants of individual components (i.e. Rep and Caspid) eliciting specific protein activity (i.e Rep and Casid protein specific activities).

Therefore the variants as claimed fails to meet USPTO written description guidelines because the invention as claimed fails to recite any specific functional limitation associated with structural variants (i.e. a specific functional activity associated with the variant of AAV4 caspid proteins).

The earlier office action provides clear *fact based scientific reasoning* that the production of AAV particle is complex as it depends upon the orchestration of various components.

For example, AAV Rep proteins encompasses Rep40, Rep 52, Rep68 and Rep 78, which are involved in regulation of replication and transcription in addition to the production of single-stranded progeny genome. Furthermore two of the Rep proteins have been associated with the preferential integration of AAV genomes into a region of the q arm of human chromosome 19. Rep68/78 have also been shown to possess NTP binding activity as well as DNA and RNA helicase activities. The Rep proteins possess a nuclear localization signal as well as several potential phosphorylation sites. Mutation of one of these kinase sites resulted in a loss of replication activity.

Similarly the capsid protein consists of three related proteins referred to as VP1, 2 and 3. These proteins are found in a ratio of 1:1:10 respectively and are all derived from the right-hand ORF. The capsid proteins differ from each other by the use of alternative splicing and an unusual start codon. Deletion analysis has shown that removal or alteration of VP1 which is translated from an alternatively spliced message results in a reduced yield of infections particles. Mutations within the VP3 coding region result in the failure to produce any single-stranded progeny DNA or infectious particles (see Spec. pages 1-4).

In the instant case, the nucleic acid sequences as claimed has been defined only by a statement of function that broadly encompasses “vector system produces AAV

particles", which conveyed no distinguishing information about the identity of the claimed genetic material, such as its relevant structural or physical characteristics.

Therefore the office clearly establish that invention as claimed fails to meet written description requirements based upon a fact based inquiry as the function of variants as claimed are generic and is not associated with any specific functional activity. Since the specification fails to disclose a representative number of species defined by structure and function, it is not possible to envision the claimed composition. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).*

In the instant case the nucleic acid sequences as claimed has been defined only by a statement of function that broadly encompasses "any variants of AAV4 capsid protein having about 90% homology to an amino acid sequence set forth in SEQ ID NO:4, and about 98% homology to SEQ ID NO: 4, 16 and 18; and any variants of AAV4 Rep protein having about 95% homology to amino acid sequences set forth in SEQ ID NO:2, 8, 9, 10 and 11 that are capable of producing AAV particle in any vector system", which conveyed no distinguishing information about the identity of the claimed genetic material, such as its relevant structural or physical characteristics. Therefore, a definition by a generic function (i.e. production of AAV particles) alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. See

also *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)).

Applicant's fundamental position fails to equate with the written description guidelines because in the guidelines, there is function correlated to the structure. The function in Applicant's claims, however, lack any association with the structure of the protein whatsoever. So consonant with the case law in Lilly, Enzo and the other written description decision of the Federal Circuit, it is clear that the current claims fail to meet the written description requirement because there is no structure function relationship which limits the genus size. The guidelines require more. They require a structure function relationship. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this genus would not be representative of other variants (as claimed by a generic function) and is insufficient to support the claim.

Claims 2-3, 6-28, 30-36 and 38-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector system for producing infectious AAV4 particles comprising AAV4 capsid proteins (SEQ ID NO: 4, 16 and 18) and AAV4 Rep proteins (SEQ ID NO:2, 8, 9, 10 and 11), does not reasonably provide enablement for any other vector system that comprises any variant of AAV4 Capsid (i.e. SEQ ID NO: 4, 16 and 18) or Rep proteins (i.e SEQ ID NO:2, 8, 9, 10 and 11) and/or any vector system that only encodes a single Capsid or Rep protein and is capable of producing the AAV particles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reason of record as set forth in the office action mailed on 09/18/07.

Response to Argument (Enablement)

The applicant argues that a proper rejection on enablement grounds depends only on the question of whether, in view of the specification and the knowledge of those of skill in the art at the time the invention was made (as evidenced by the complete

record in this application plus the body of knowledge available in the art at the time of filing), the compositions of claims 2-3, 6-28, and 30-42 could be made and used (for any specific and substantial purpose) by those of skill in the art without the need for undue experimentation. The applicant continues that the present claims and corresponding enablement rejection closely parallel the situation presented in Wands since the art of producing the presently claimed nucleic acid compositions encoding the genus of AAV4 peptides is routine experimentation in the art of recombinant nucleic acid and peptide design, even though it may seem complex. Furthermore, the fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. See M.I. Z v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

The applicant argues that the claims do not read on a vector system that comprises "any and all functional equivalent variants of Rep and Capsid proteins". The applicant argues that the knowledge and skill available based on prior studies of AAV2 vectors was such that the skilled artisan would be able to assay candidate AAV4 vector systems for the ability to produce AAV particles using routine experimentation. This screening process would be considered routine based on the quantity of experimentation necessary, the amount of direction or guidance presented, the presence of working examples, the nature of the invention, the state of the prior art, and the relative skill of those in the art.

The applicant continues that the function of sequences at least 90% identical to a known protein with a described function is highly predictable. It is generally understood that a molecule with 70% or greater homology to a known sequence will have the essential physical properties of the identified structure.

The applicant believes that applicants would expect with a very high level of certainty that any given sequence would function, and the skilled artisan would likely never pick a sequence that would not function. Further, while the skilled artisan has a high expectation that any given sequence having 90% identity would function, if needed, it is routine experimentation for one skilled in the art to test such variants to determine if they fit into the claimed homology and to assay said variant for functionality (e.g., AAV

particle formation). The applicant concluded that the assaying of candidate vector systems for the ability to produce AAV particles, also requires no more than routine experimentation since there is a high level of predictability that a given peptide within the defined genus will function.

However this is found not persuasive in view of written description rejection above as the specification fails to disclose a representative number of species defined by structure and function (i.e. Capsid and Rep specific functions). Therefore, it is unclear how one skilled in the art use the invention as claimed. The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount. of experimentation, which requires the identification and characterization of any and all variants of AAV4 Capsid (i.e. SEQ ID NO: 4, 16 and 18) or Rep proteins (i.e SEQ ID NO:2, 8, 9, 10 and 11) that are capable of producing the AAV particles alone or in any combination. In instant case applicant only disclosed AAV4 genome (AAV4 2260-4467nt of SEQ ID NO:1), AAV4 Rep proteins (SEQ ID NO(s): 2, 8, 9, 10 and 11) and AAV4 Capsid proteins (SEQ ID NO(s): 4, 16 and 18); and proposes to discover other members of the genus.

In instant case screening of any and all natural and non-natural variants, wherein at least 10% of residues are added substituted and/or deleted at random in the disclosed SEQ ID NO(s) is not considered routine in the art. The applicant fails to point out where in the specification there is support for extensive making and testing of any and all natural and non-natural variants as claimed. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 10% amino acids are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further undue experimentation, since the specification can not be relied on to teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed telomerase activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd

1400 (Fed. Cir, 1988). In addition, it is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

The variation as claimed also encompasses the conserved motifs that are germane to native biological activity of the encoded protein. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The variants as claimed are mere hypothetic because no specific biological function has been assigned therein. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. The applicant has not presented enablement commensurate in scope with the claims. Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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